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PhRMA

July 8, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-0571; Draft Guidance for Industry on Drug Substance Chemistry, Manufacturing and Control Information; 69 Federal Register 929 (Jan 7, 2004)

Dear Sir/Madam:

The following comments on the above draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Investing more than $30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA appreciates the significant effort by the Food and Drug Administration (FDA) in preparing this draft guidance. However, we feel that many sections of the document are inconsistent with the FDA's current philosophy of a risk-based, science-based approach to drug regulation. PhRMA's major concerns are over the starting materials section (Attachments I and II) and the apparent increase in level of detail requested in many sections throughout the guidance.

To address the starting material issues, PhRMA proposes an alternative approach to selection of starting materials. Regarding the increased level of details requested, PhRMA recommends that the FDA clarify when listed items are included for the applicant's consideration and when items are expected to be included for most drug substances. This clarification would allow applicants to use a science-based, risk-based approach to determine the amount and level of detail of information provided in the various chemistry, manufacturing and controls (CMC) sections

In addition, PhRMA believes more discussion between industry and the FDA is needed on conceptual issues and that a Joint Industry/FDA workshop or meeting on these issues is needed prior to a final guidance being issued.

The following specific comments are given for consideration in preparing the final guidance. Our conceptual concerns are provided in this cover letter while detailed line-by-line comments are provided in the attachment table.

Conceptual Concern #1 –Guidance on Selection of Starting Materials (Attachments I and II) is overly restrictive, not science-based and should be rewritten.

PhRMA endorses the FDA position in lines 1691-1694 and in 1727-1733:

"FDA will consider the justification provided to support a proposed SM as well as other relevant information such as the proposed SM specification and controls on manufacturing steps downstream from the proposed SM when evaluating the appropriateness of a proposal to designate a chemical as a SM."

"These principles are intended to assist an applicant in proposing starting materials at a point in the process that ensures:

1. *Sufficient information is submitted in the application for FDA to evaluate the safety and quality of the drug substance*
2. *Future changes in the manufacture of the SM are unlikely to affect the safety or quality of the drug substance"*

Pharmaceutical companies currently have very different starting material (SM) selection strategies. All of these different strategies are legitimate and assure product quality when supported by data, a strong scientific rationale, and internal quality assurance systems. This flexibility regarding starting material selection needs to be retained in any future guidance.

It is PhRMA's belief that Attachment 1 in the Draft Guidance does not support the stated FDA goal of appropriate and justified starting material selection. Further, it is not scientifically justified and needs to be substantially reworked for the following reasons:

- Absence of the science-based approach currently advocated by the Agency;
- Absence of the risk-based approach currently advocated by the Agency;
- Inconsistencies with relevant ICH Guidances (Q7A, Q3A, etc.); and
- Many of the internal quality assurance systems, such as vendor qualification, practiced by industry are not referred to in the guidance.

Selection of SM is a fundamental part of a holistic process control strategy, which assures active pharmaceutical ingredient (API) quality. It is the responsibility of the Applicant to select the SM using science and risk-based criteria. The Applicant should develop a robust SM specification, which together with the use of appropriate analytical methodology generates data to support the SM selection.

PhRMA has the following specific feedback on the starting material attachments:

Propinquity (lines 1740-1766 & 1907-1911)

Some "bond forming" steps, which count towards propinquity, may not result in a purge of impurities from the process. Other processing steps, which would not count towards propinquity, such as a salt formation, probably WILL result in a purge of impurities from the process and will consequently improve quality assurance. Therefore, simply counting the number of process steps downstream from SM to final intermediate does not assure API quality. What matters is the scientific understanding and the design of the process to optimize appropriate

purification capability from the SM to the API, not the number of intervening processing steps.

Concerns about the risk of introducing unknown impurities which have the potential to affect API quality are legitimate. However, this concern should be addressed by means other than propinquity, e.g., by control of unidentified impurities in the SM specification, by use of discerning analytical methodology and by use of good manufacturing practices (GMP) quality systems such as vendor qualification procedures.

Isolated and Purified (1768-1773 & 1913-1917)

The quality of the SM has to be controlled by appropriate acceptance criteria and analytical methodology, described in the SM specification. The use of the term "purified" to describe a SM is irrelevant to it's' suitability for use.

On the same basis, the physical form of the SM is also irrelevant to its suitability for use. The applicant should therefore have the option to select a SM that is a liquid or a solution.

Carry-Over of Impurities & Specifications (lines 1775-1797, 1843-1867 & 1919-1957)

Current industry practice, consistent with ICH Q3A(R), is that impurities in API which originate from SM should be qualified and appropriate specifications should be established. This section should be revised to refer to ICHQ3A(R).

Complexity of Structure (1799-1818)

Analytical methods used to determine SM quality need to be capable of distinguishing between potential isomers and analogs of "complex" SMs. It is the applicant's responsibility to use the most appropriate and best available analytical method to do this. Since contemporary analytical technology is able to fully characterize complex structures, degree of complexity itself should not be a SM selection criterion.

Attachment 2: Starting Materials of Plant and Animal Origin

For a semi-synthetic drug substance, which is manufactured via a multi-step chemical synthesis from a biological source material, a chemical compound downstream from the natural source may be an appropriate SM, provided that it is stable, well characterized and meets appropriate specifications. It is agreed that the origin biological source may need to be identified.

Starting Material Definition (Glossary lines 2234-2239)
The definition in the Draft Guidance should be replaced with the definition for API Starting Material from ICH Q7A.

PhRMA proposes the following alternate SM selection and justification principles:

As stated above, pharmaceutical companies currently have very different SM selection strategies, all of which are legitimate and assure product quality with appropriate data and quality systems support.

As an alternate to the selection and justification criteria in the Draft Guidance, PhRMA proposes an alternative approach, which allows flexibility on the part of the Applicant while assuring product quality through the use of scientific and risk-based considerations outlined below. Simply put, the applicant should be able to select and justify an "early" or a "late" SM, but with the implicit, risk-based, assumption that late stage SM's may carry with them an increased risk of adversely affecting API quality (e.g. by introduction of unidentified impurities in SM). It is the PhRMA position that these potential risks can be mitigated by additional controls, which need to be put in place by the Applicant as a consequence of selecting a late stage SM.

This PhRMA proposal on SM selection and justification is qualitative and requires judgment on the part of the applicant and the Agency. It is a framework for science and data-driven discussions on SM selection. It is proposed that these discussions take place at the end of phase II meeting between the applicant and the Agency.

The following are suggested industry considerations (not requirements) for selection and justification of SM's:

1. SM is well characterized*;
2. SM stability is understood;
3. Appropriate, discriminating analytical methodology is used to determine the quality of the SM;
4. SM specifications are appropriate to assure quality of API;
5. The impact and effect of SM quality on the API quality is understood and controlled; and
6. Downstream purification steps are recognized with *downstream control gates* (in-process controls) to "build in" and assure API quality during manufacture.

* Note that the physical form of the SM is irrelevant to determine its suitability for use. Also, an API may be an appropriate SM for a new downstream synthesis.

Additional considerations for "late" SMs include:

1. SM synthetic route information e.g. flow sheet;
2. Names and site addresses of qualified SM suppliers;
3. Post-approval SM changes e.g. new SM supplier, new SM process, will be managed and qualified; and
4. Analytical methodology and specifications will need to be more discerning and more discriminating compared to an early-stage SM:
    a. Trend towards "API-like" specifications;
    b. Specification for unknown impurities.

PhRMA recognizes that these proposed alternative SM selection and justification considerations are significantly different from those proposed by the Agency in the Draft Guidance. PhRMA would therefore welcome the opportunity to meet with the Agency to discuss this issue.

Conceptual Concern # 2 – The increased level of detail and amount of information requested by the draft guidance as compared to previous guidance and accepted industry practices is not consistent with a risk-based, science-based approach to review of CMC information.

The draft guidance appears to increase the level of detail of several sections over currently accepted practices. Attachment I provides specific comments on individual lines of the guidance where PhRMA considers the increased level of detail requested to be unnecessary, unduly burdensome and of little or no added value.

PhRMA has particular concerns over the Description of the Manufacturing Process and Process Controls in Section S.2.2. This section seems to have dramatic increases in the level of detail requested. The draft guidance requests a detailed flow chart in addition to a detailed narrative description of the process. Information is requested on all process controls (critical and non-critical) and the definition of process controls is extremely broad.

If all of this information is included with every application the burden on industry and reviewers will be significant. In most cases, the increased information requested, for example temperature and humidity controls, may not be relevant to a particular manufacturing process.

In addition, the level of detail requested is often inconsistent with current post-approval change guidances. For example, lines 453 and 454 request details on type of equipment used in the process whereas *BACPAC I: Intermediates in Drug Substance Synthesis* (BACPAC I), successfully implemented since 2001, would not require reporting of changes in equipment prior to the final intermediate.

BACPAC I acknowledges that many changes prior to the final intermediate have a very low risk of adverse impact on the quality of the drug substance. Providing additional details on these early process steps in the initial NDA filing on these topics similarly does not improve the quality of the drug substance. However, this increased detail does make submissions longer and creates additional work for industry and FDA reviewers.

This draft guidance does include the standard disclaimer that different approaches which satisfy the applicable statutes and regulations are acceptable. However, there are no clear statements in the text of the guidance supporting an applicant's use of risk-based, science-based evaluation to determine what specific items to include or exclude in a particular filing.

PhRMA feels that these detailed lists of items (e.g. lines 413- 430, 448-472 and 507-516) create an expectation that all of this information is relevant for every application. This does not allow for flexibility to tailor the information provided to the items and level of detail needed to facilitate a thorough and efficient review of the process and to establish the quality of the drug substance produced by that process.

As noted above, PhRMA recommends that additional qualifying language be added throughout the document to clarify where specific detailed lists are included for consideration and that an applicant can use a risk-based and science-based judgment to determine which items are relevant to the process and drug substance being described.

Conceptual Concern # 3 – Section S.2.4 does not provide applicants with sufficient flexibility to select and justify "critical" parameters, controls and material tests based on science and risk.

PhRMA endorses the definition of "critical" provided in the glossary. This definition correctly limits "critical" to those process steps or process controls that must be controlled within predetermined limits to ensure that the **drug substance** meets it specification. This definition clearly excludes process controls that are implemented to ensure intermediates meet specifications or are controlled to ensure non-quality related aspects of the drug substance such as yield.

However, PhRMA disagrees with the approach of section IV. D – Controls of Critical Steps and Intermediates (S.2.4). Lines 768 – 776 state that "all critical operating parameters, environmental control, process tests and **all** tests performed on intermediates, postsynthesis materials and unfinished drug substances should be listed and their associated numeric ranges, limits, or acceptance criteria should be identified." This paragraph goes on to suggest that applicants should list non-critical tests on materials separately to distinguish them from critical tests.

PhRMA believes that these lines should be deleted and that the applicants should be responsible for selecting and justifying the controls, parameters, and material tests that are critical to the quality the drug substance. As stated in Lines 778 –787, these critical items should be described and justified in Section S.2.4.

In addition PhRMA feels that the inclusion of the new terms "Postsynthesis Materials" and "Unfinished Drug substance" creates confusion and that these terms should be removed. The addition of these new terms in lines 838 - 863 coupled with the language in lines 768-776 creates a new requirement to file information on testing these late stage materials even if they do not impact the quality of the final drug substance. PhRMA acknowledges that these terms were an attempt to clarify the various stages of materials after the final intermediate but PhRMA believes the creation of new terms is unnecessary.

PhRMA recommends deleting lines 768 – 776 and lines 838 – 863 and rewriting the section to clarify that the applicant is responsible for selecting and justifying "critical' parameters, controls and material tests based on the definition of "critical" provided in the glossary.

PhRMA also believes that more discussion is needed between the industry and FDA regarding the selection of critical parameters, controls and materials tests based on science and risk. An open exchange of ideas and practical experiences with this issue would benefit both industry and FDA.

Conceptual Concern # 4 – The examples of reprocessing, reworking and other operations are not consistent with ICH Q7A definitions for these operations.

A definition of reprocessing is not included in the glossary of this guidance. Lines 566 – 570 provide a definition that is consistent with ICH Q7A and allows for repetition of filed process steps. However, lines 577-578 state that repetition of multiple reaction steps is considered reworking. P*h*RMA recognizes that repetition of multiple reaction steps is generally discouraged but feels that in certain cases it is justifiable scientifically and is within the definition of reprocessing.

Similarly, lines 657 – 661 classify processing material to bring it back into conformance with its specification after release as "Other Operations." P*h*RMA members feel that if the steps taken to return the material to its specification are part of the filed process, this should be considered reprocessing. The fact that a Quality Control lab has "released" the material should not exclude this from the reprocessing definition.

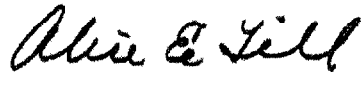
With any reprocessing, companies are required under GMPs to ensure that the reprocessing is appropriate to correct the problem with the material. For example, if a hygroscopic drug substance fails its water content specification after time, it is appropriate to dissolve and recrystallize the material according to its filed process. However, a company must consider whether potential impurities formed by reaction with the increased water content are removed by the filed process and are detected by the analytical controls.

P*h*RMA members feel that the definition of reprocessing should be consistent with the definition used in Q7A. The FDA should not carve out new exceptions to that definition for filing purposes as this will, in the long run, generate confusion in both the filing and post-approval application phases. Field investigators, who have an opportunity to review supporting data and scientific rationale for each reprocessing, should remain responsible for assessing companies' reprocessing practices.

As stated earlier, P*h*RMA believes more discussion between industry and the FDA is needed on the above conceptual issues and that a Joint Industry/FDA workshop or meeting on these issues is needed prior to a final guidance being issued.

Additional specific and detailed comments are provided in the attached word table. However, we have not included any detailed comments on the Starting Material Attachments, as we believe these should be rewritten. Please contact me if you need further assistance or have any questions regarding these comments.

Sincerely yours,



Alice E. Till, Ph.D.

CC S. Miller; C. Joneckis; D. Bensley

Attachment

PhRMA Detailed Comments to
Draft Guidance for Industry – Drug Substance Chemistry, Manufacturing and Controls Information
(Docket Number 2003D-0571 – December 2003)
July 8, 2004

Line Number(s)	Comment or Suggested Rewrite (Bold text indicates text added to current language in guidance document, strikethrough indicates text to be deleted)	Rationale
48	Modify line to read "Drug substances manufactured by chemical synthesis, **except as noted below.**"	Peptides and oligonucleotides can be considered a subset of APIs manufactured by chemical synthesis.
52	Bullet 4 should be modified or deleted.	Bullet #4 does not describe a type of drug substance.
59	Synthetic Peptides and synthetic oligonucleotides should be included.	Synthetic peptides and synthetic oligonucleotides are produced by standard chemical reaction steps; the materials employed are well-characterized standard materials. Thus, no biological system is involved for generation of these molecules. Accordingly, they should be treated as chemicals.
66	It is unclear why fermentation products are universally excluded from the guidance.	Fermentation processes are no longer uncommon, are generally well understood and controlled, and could potentially be the subject of this guidance.
81	Add sentence **"In particular, application of risk-assessment principles, which are in line with FDA's Risk Based Approach, can justify a different approach."**	Application of risk-based approach principles should be explicitly allowed.
109-110	~~" However, an applicant should still provide information to address some of the drug substance subsections."~~	Duplicate information should be limited to preclude unnecessary work by the NDA holder and by the FDA.
140	Line 140 should read "... for approval under the application. **It may be appropriate to designate certain sections or subsections as "not applicable" in the submission.** Information should be provided..."	It is unrealistic to expect that all subsections will apply to all applications for API approval.

222 -285	Delete lines	If a DMF is used to submit Drug Substance information, this section recommends that information be repeated in the NDA. We do not agree with this approach. It is important not to duplicate information in the DMF and the application, requiring updating of both a DMF and an application when post-approval changes are made and increasing compliance risks. Additionally this is inconsistent with 314.420 that allows for use of DMFs to submit information. Also, in some cases the proprietary information may not be available to the applicant.
293	General comments: 1. For clarity, Section III should be headed "Content of a CTD-format CMC (Drug Substance) section" and the following sections, from III.A to IX.C, should be numbered and headed according to the sections of CTD-Q Module 3.2.S. 2. Some information might not be required for already marketed drug substances, e.g. substances used for generics (e.g. § S.2.5 & § S.2.6, Process development, full structural analysis, batches used for clinical trials, analytical development....). This should be clearly indicated.	
301	Change line 301 to read: "Any codes, or abbreviations ~~or nicknames~~ used in the application. . ."	The term 'abbreviations' covers 'nicknames.'
352	Biological activities should be added to the list specific to naturally derived protein drug substances on lines 357 to 359, and qualified on line 352 for synthetic drug substances as follows:Biological activities (for synthetic peptides).	Protein drug substances are tested for biological potency, but most drug substances manufactured by chemical synthesis are not.
363-365	"Detailed information on the characterization (e.g. X-ray powder diffraction data, thermal analysis curves) of these and other physical forms ~~and conditions required to produce one form or another should~~ be provided in S.3.1."	In many cases it might not be possible to produce every single modification in pure form due to e.g. hygroscopicity, instability etc. Studies to produce modifications can be reported.
376 - 378	"The name, address, and manufacturing ~~responsibility~~ operation should be provided for each firm (including contract manufacturers and testing laboratories) and each site (i.e., facility) that will be involved in the manufacturing or testing of **intermediates and** the drug substance."	The meaning of manufacturing 'responsibility' is ambiguous. Section S.2 should also include sites where intermediates, post-synthesis materials, and unfinished drug substances are manufactured and tested.
378	Please clarify if testing laboratories mean both release and stability.	For clarification

382	"The addresses should be for the location where the relevant manufacturing or testing operation will be performed. Addresses for corporate headquarters or offices need not be provided. ~~Building numbers or other specific identifying information should be provided for multifacility campuses.~~"	Building numbers should be required only for sterile/aseptic operations. According to Changes to an Approved NDA or ANDA, moving between buildings within a site does not have to be reported except for sterile/aseptic processing of sterile drug substances. Therefore, including building numbers in the initial application is unnecessary in most instances.
385	"For sites processing sterile drug substances, the sterile processing area ~~(e.g., room)~~ should also be included."	Room designation is too detailed. Identifying the sterile processing area should be sufficient.
389- 391	"To facilitate preapproval inspection related activities, it is recommended that the name, telephone number, fax number and e-mail address of a contact person be provided for each site listed in the application, **this information may be listed in this section or elsewhere in the application such as the 356H form or the administrative information section.**"	Requirement for contact name and telephone number for facilities are more appropriately given in the accompanying Form 356H, not in the original application. If they are provided in the body of the application it should be clear that there is no requirement to update this information after the original filing.
392	"Facilities should be ready for inspection when the application is **accepted for submission by FDA, or FDA should be notified when a facility will be ready for inspection.**"	FDA PAI's do not typically occur before formal acceptance of the filing; current forms allow specifying of inspection-ready dates. This practice should not be changed.
399	"A flow diagram and a ~~complete~~ description of the processes and **critical** process controls ... "	Listing of all process controls is not useful to a reviewer and would only cause a more lengthy process description with no added value. Many controls are for safety, environmental, or business purposes and do not affect quality. Also the term "complete" is difficult to interpret. The regulations are already clear that the applicant must describe the process in sufficient detail for the reviewer to assess the safety and quality of the drug substance.
402, 2115	"If justification for an alternative process is warranted, the information should be included in S.2.2 (e.g., comparative impurity data on intermediates) or can be cross- referenced if provided elsewhere in the application (e.g., S.4.4)."	The definition of alternate process in the glossary should be made more specific and examples should be provided.
410	The entire manufacturing process should be depicted (i.e., starting materials through **final** drug substance ~~release~~ testing).	For clarification

411-436	The flow diagram should provide a summary description of the process, strike lines 411-436 and include a clearer description of whether they want a structural flow diagram or a block flow diagram.	The content of the Flow Diagram should be sufficient to give the Agency reviewer an overall view of the processing to be conducted and the chemistry. Other information is better reserved for the narrative description where the applicant can provide the necessary detail regarding critical operations, critical control parameters and the manner in which they are monitored and controlled in the processing. If these lines are not deleted we have the detailed below requests for specific changes.
422 / 841	"Chemical structure (including stereochemical configuration where applicable) or biological identification of starting materials, intermediates, structurally complex reagents, ~~postsynthesis materials,~~ and the drug substance."	. What is FDA's rationale for the inclusion of two new terms of; 'Post synthesis materials' and 'Unfinished Drug Substance?' PhRMA believes these new terms are unnecessary and confusing.
427	" **Critical** ~~O~~operating parameters (e.g., temperature, pH, pressure) for each manufacturing step".	While ensuring appropriate regulatory control this will minimize unnecessary post approval submissions. The detail requested here is at times excessive and appears to be moving in the opposite direction with FDA's current thinking on science and risk based regulatory processes. Submission of excessive non-critical detail could result in difficulty in later making improvements or changes.
429	"An indication of whether intermediates are used in situ or isolated before being used in the next reaction step and which intermediates are considered the final intermediates"	The definition of Final Intermediate in BACPAC I is clear and should be used. Thus identification of the identification of the final intermediate on the flow chart should not be necessary.
430	"~~Expected yield (percent) for each reaction step~~"	It is redundant to have the yield information in both the flow chart and the narrative description. It should only be in the narrative description of the process.
440	"A narrative description of the manufacturing process that represents the sequence of manufacturing steps undertaken ~~and the scale of production should be provided.~~"	Changes to the manufacturing batch size need not be reported per current guidance; thus this information should not be required in the application.

442	"The description should identify all **critical** process controls and the associated numeric ranges, limits, or acceptance criteria. ~~Furthermore, any process controls that are considered critical process controls should be highlighted.~~ See below for additional information on **critical** process controls."	Listing of all process controls is not useful to a reviewer and would only cause a more lengthy process description with no added value. Many controls are for safety, environmental, or business purposes and do not affect quality.
450	"Starting materials or intermediate used in each step, with chemical or biological names and quantities **or molar ratios** specified **if critical** "	Absolute quantities do not necessarily add value. Molar ratios are often more meaningful.
454	"Type of equipment (~~e.g., Centrifuge) used,~~ including materials of construction) ~~when critical~~ **if critical to control of material quality**"	To specify equipment not critical to the control of quality would add no value to the submission but would increase the size of the document and add burden to industry and reviewers. Additionally, most changes to equipment post approval are not reportable thus detailing them in the original submission is valueless.
455	"~~Identification of the manufacturing steps that are considered critical~~"	Identification of 'critical steps' is considered to be irrelevant. What is important is identification of critical controls.
457	"~~All~~ **Critical** process controls and their associated numeric ranges, limits, or acceptance criteria, ~~with critical process controls highlighted.~~"	It should only be necessary to include critical process controls in the application; Tests used only for process information, troubleshooting, economic reasons, environmental (EPA) reasons, etc. and not needed for quality control, should not be reported.
460	"Identification of intermediates, ~~post-synthesis materials, and unfinished drug substance~~ **that are routinely tested in connection with critical process controls** (details should be provided in S.2.4)."	It should be clarified that FDA does not intend to require the manufacturer to register any and all testing that it may choose to do for internal information purposes.

465-466	"Identification of manufacturing steps that use ~~recovered~~ **recycled** solvents or auxiliary materials (see section IV.B.3.c)"	Recycled solvents/reagents are those reused in the process without purification. Therefore, designating where recycled materials are used is appropriate. Recovered solvents/reagents are purified such that they meet the same specifications as for new material as described in Section S.2.3, Control of Materials. Therefore, distinguishing the place where these materials are used is unnecessary.
470	"Identification of processes that involve combining ~~intermediate or drug substance batches,~~ drug substance and a diluent, or two or more drug substances"	This is confusing. Combining intermediates for the next process step is common practice in API manufacturing. Also blending of tailings and dryer loads are common practices which are routinely reviewed during FDA inspections. The major issue with blending is maintaining traceability of batch histories after blending. If this is addressing blending this should be a cGMP issue not a filing issue.
472	"Yield ranges (weight and/**or** percent) for each manufacturing step **resulting in an isolated intermediate or the final API. Typical yields are provided for information only, and are not considered registered parameters; explained deviations from these typical yields generally need not be considered operating outside the registered process.**"	The yields for individual steps are often not critical quality-indicating parameters, and may be impacted by a number of external parameters. If yields are requested for information, it should be clear that deviations from the yield generally need not be considered a regulatory deviation.
488-489	"A ~~statement~~ **risk analysis** should be provided ~~that~~ **if** bovine-derived materials from bovine spongiform encephalopathy (BSE) countries ... Are ~~not~~ used or manipulated in the same facility."	The acceptability of use of such materials in the same facility depends on various factors such as the source and kind of material, facility design, equipment, removal/inactivation steps, cleaning, cleaning validation data etc. If materials are used then the risk analysis should be provided.
496-498	"**Significant** Differences between the manufacturing process described in S.2.2. and the manufacturing process used to produce the primary stability batches should be discussed in S.2.6."	Adaptation to wording in line 908
499	"**Critical** Process Controls"	Only 'critical process controls' should have to be reported. This will eliminate detail that is not critical to quality.

501- 507	Delete lines 501 to 517 entirely.	Process controls are defined in the Glossary. This section should be clear as to which process controls are to be filed. If the section is not deleted, our specific comments on individual lines are provided below.
508 - 517	Each of the four bullets should be updated to reflect the need for only those operating parameters, environmental controls, process tests and in-process tests which are critical to assure intermediate or API quality.	This request is consistent with the theme that the manufacturing process description should reflect only critical information.
510-511	"Environmental controls — conditions associated with the manufacturing facility **for aseptic or terminally sterilized drug substances** (e.g., temperature, humidity, clean room classification)"	Environmental Controls for non-sterile operations are not appropriate for inclusion in the application. These controls are evaluated during routine GMP inspections.
521	"~~All~~ **Critical** process controls, ~~critical or otherwise,~~ should be included in the description of the manufacturing process."	Listing of all process controls is not useful to a reviewer and would only cause a more lengthy process description with no added value. Many controls are for safety, environmental, or business purposes and do not affect quality.
537	"~~All of~~ the **critical** operating parameters, environmental conditions, and process tests that ensure each critical manufacturing step is properly controlled should be specifically identified ~~as critical~~ **either** in the flow diagram ~~and~~ **or the** description of the manufacturing process in this section of the application (S.2.2) and in S.2.4."	Minimize duplication of information.
540	"**Tests on intermediates required to ensure the quality of the final drug substance** ~~All tests on intermediates, postsynthesis materials, and unfinished drug substance~~ should be listed in the description of the manufacturing process in S.2.2 and described in S.2.4."	Only those tests and controls that have been demonstrated, using appropriate scientific methodology and risk assessment, to be critical should be part of the file.

545	Add the following statement. **"Operating conditions may occasionally deviate from the NDA description. In accordance with cGMPs, the manufacturer should document and explain any deviation. Any critical deviation should be investigated. Occasional, minor deviations need not be reported to the NDA."**	The statement regarding minor deviations in the 1987 guidance is no longer present. Industry would like clarification that the investigation of deviations is covered under GMPs and is not a registration issue.
547	The word 'Critical" should be moved to the top line of each box in the third tier of this figure. Delete the phrase "if critical" from the bottom line.	Consistent with earlier arguments. Non-critical controls should not be included.
547	The objective of Figure 1 is not clear. Why has S.3 "Control of materials" been excluded?	Clarity
547-549	Remove the use of shadow print.	The diagram is difficult to read.
552	"Reprocessing, **recycling and regeneration** should be described in S.2.2, when appropriate **as described in the final paragraph of section "a" below**. When used, reworking, ~~recycling, regeneration,~~ and salvaging operations should be described in S.2.2. These operations should be adequately controlled to ensure that there is no adverse effect on the identity, quality, **or** purity~~, or potency~~ of the drug substance. "	Clarify that only frequent reprocessing steps need to be filed in the application. In general reprocessing is not required to be described in the application. Also recycling and regeneration should not be filed if the recycled solvent or regenerated materials meet the specifications for described in the application.
555	"Moreover, reprocessing and reworking operations should be capable of **bringing one or more quality attribute of the material within the acceptable range without causing significant, adverse change that could lead to a specification failure for the material.** ~~of producing an improvement in one or more quality attributes without having an adverse effect on others.~~	The current sentence is too restrictive. It would suggest that, for example, a slight increase in moisture, within the acceptance ranges for the process, could prevent the implementation of a reprocessing to reduce impurity levels within their acceptable range.

557	~~"Information (e.g., comparative analytical data) to support the appropriateness of these operations should be included in S.2.2 or can be cross-referenced in S.2.2 if information is provided elsewhere in the application.~~ If the operation involves critical manufacturing steps or intermediates, information should also be provided in S.2.4. ~~However, validation data, when warranted to support the operation, should be provided in S.2.5. (see section IV.E for possible situations when process validation information is warranted.)"~~	Supporting information should only be provided in the filing on reworking and salvaging operations that involve critical steps. If the step is not critical the rework or salvage should be described in S.2.2 but supporting data should not be included in the filing.
567-576 602-605	Definitions for reworking and reprocessing should be added to the glossary. We support the definitions provided in the ICH Q7A.	For clarification
569	"Reprocessing is the introduction of an intermediate or drug substance, including one that does not conform to a standard or specification, back into the process and repeating ~~a crystallization or other~~ **an** appropriate chemical or physical manipulations (e.g., distillation, filtration, chromatography, milling, **crystallization**) that are part of the approved manufacturing process."	Crystallization should not be treated differently then any other process step.
573	"Continuation of a manufacturing step after a process test has shown that the step is incomplete is considered to be part of the normal process and is not reprocessing. **Introduction of unreacted material back into the process is reprocessing.** Repetition of a single reaction step should be carefully evaluated with respect to the potential formation of by-products and over-reacted materials."	Introducing unreacted material back into the process - ICH Q7A 14.22 - should be included here. In addition, it should be stated that nonchemical enabling steps which are necessary to reintroduce the material into the established process, such as dissolving it in the original solvent, or filtration to eliminate unwanted solid materials, are allowed.

577	"Repetition of multiple reaction steps ~~is~~ **should be** considered **very carefully** ~~to be reworking, rather than reprocessing (see section IV.B.3.b)~~ **because the material to be re-introduced into the process may not be similar to the original reactant. Repetition of multiple reaction steps is discouraged."**	We do not agree that repetition of multiple steps contained in the process should always be considered reworking. We agree that re-introduction of an intermediate through multiple reaction steps without thorough evaluation of the impacts to substance quality attributes should be avoided.
579	Add the following at the end of this paragraph: **"Non-chemical unit operations which are not part of the routine processing can be conducted during reprocessing. Examples include dissolution in the filed solvent and filtration after dissolution."**	These operations do not introduce new chemical steps or reagents to the operation and are low risk. They should be allowed as enabling steps to reprocessing.
580	Add the following text: **"Reprocessing a drug substance, after it has been released by the quality control department, to bring the material back into conformance with its specification may be allowable in certain instances. Examples include reprocessing a hygroscopic material to lower water content, milling to meet a different particle size specification, reprocessing of heels or repurification of aged material to conform to approved specification."**	Reprocessing after release should not be treated as rework. The same principles apply to appropriateness of reprocessing before and after release.

586	"However, if there is a significant potential for the reprocessing operation to adversely affect the identity, strength, quality, **or** purity~~, or potency~~ of the drug substance, the reprocessing operations should be described and justified in this section (S.2.2) of the application."	Potency is not an attribute of a drug substance.
588	"For example, CDER would consider reprocessing proteins, **as covered in this guidance**, to be reprocessing operations that should be described in the application."	Clarity as to scope of this guidance
604	~~"Repetition of multiple reaction steps is considered to be reworking because the material to be reintroduced into the process is not similar to the original reactant. Repetition of multiple reaction steps is discouraged because of concerns relating to unexpected impurities and degradants."~~	Repetition of multiple steps is discouraged but should not be defined as reworking.
611	~~"In general, reworking operations are developed postapproval, and the application is updated through submission of a prior approval supplement that provides test results and, if appropriate, to evaluate the effect of the reworking procedure on the identity, quality, purity, or potency of the drug substance."~~	Designation of post-approval requirements is contained in other guidance.
622	"The ~~use of recovered solvents and~~ recycling of filtrates (mother liquors) to recover reactants, intermediates, or drugs substance, including for the purpose of producing or isolating additional crystals (i.e., second crops), should be described in S.2.2."	If recovered solvents are returned to virgin condition, no reporting should be required.
625	"Recovery operations should be adequately controlled so impurity levels ~~do not increase over time~~ **meet specifications**."	Applicant must meet the appropriate specification (for the intended use) to allow the material to be used again.

627-636	Replace the entire paragraph with the following sentence. "**The use of recycled solvents/reagents, including the point at which they might be used in the process, should be included in the description of the manufacturing process. The use of recovered solvents that meet the specifications described in Section S.2.3. need not be described in Section S.2.2. Solvents recovered from other sources (or processes) should be specified in S2.3.**"	As noted above, recycled solvents/reagents are those reused in the process without purification. Therefore, designating where recycled materials are used is appropriate. Recovered solvents/reagents are purified such that they meet the same specifications as for new material as described in Section S.2.3, Control of Materials. Therefore, distinguishing the place where these materials are used is unnecessary. Definitions for recycled and recovered solvents should be added to the glossary.
639	"Recycling of filtrates should be included in the description of the manufacturing process if these operations are performed. ~~Information should be provided on the maximum number of times material will be recycled and for the process controls for such operations.~~ Data on impurity levels should be provided to justify recycling of filtrates."	It should not be necessary to specify the maximum number of times a recycle can be used, assuming the recycled filtrate has meaningful specifications established and continues to meet these specifications.
647	"The regeneration of materials such as column resins and catalysts should be described in S.2.2. if these operations ~~are performed.~~ **are critical.** The **critical** process controls for regeneration operations should be provided."	The process controls for column, resin or catalyst regeneration may improve operational efficiency but are not always critical to quality.
655	"e. ~~Other Operations~~ **Salvage**"	We recommend below moving reprocessing after release, so this section now only addresses salvage.

657	"The recommendations for reworking apply to ~~(1)~~ **salvaging operations such as** recovery of drug substance from drug product or drug product in-process materials ~~or (2) a drug substance, after it has been released by the quality control department, that undergoes processing to bring the material back into conformance with its specification (e.g., purification of aged material to decrease the level of degradation products to conform with the approved acceptance criteria)~~. The recommendations for ~~reworking~~ **salvaging** operations apply irrespective of whether the operation repeats steps that are part of the approved manufacturing process (see section IV.B.3.b)."	Reprocessing after release should not be considered reworking. This should be moved to the reprocessing section.
669	"Information on the materials (starting materials, reagents, solvents, auxiliary materials, and diluents) that will be used to manufacture the drug substance or derive it from a biological source, including purification, should be provided in S.2.3."	Add definitions for reagent, solvent and diluent to the Glossary.
673	Add principle of PQIT and sunset tests for Section S2.3 Starting Materials and Raw Materials.	This concept seems very appropriate to raw materials and starting materials as the new guidance is asking for additional tests and specs for Starting Materials and Raw Materials.
675-677	~~"When appropriate, specific tests and acceptance criteria to control microbial contamination should be included in the specification for materials used to manufacture drug substances.~~ **For those cases where the sterility of a sterile API might be affected by a specific raw material, specific tests and acceptance criteria to control microbial contamination should be included in the specification for those materials, when used to manufacture sterile drug substances."**	Original statement was unclear.

683	~~"The starting material for application purposes can differ from the active pharmaceutical ingredient (API) starting material, which marks the point in the manufacturing process from which appropriate GMP should be applied (as defined in ICH Q7A: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients)."~~	Q7A intended for the application to define the Starting Material for synthetic processes.
687	"In general, the starting material **for filing purposes** and API starting material **as defined by Q7A** ~~should be~~ **are** the same for a synthetic drug substance."	There is no need for difference with Q7A since the starting materials should be agreed with the reviewer, preferably at the End of Phase 2 meeting.
690	"However for a drug substance derived from a biological source, the starting material (e.g., plant) and API starting material (e.g., extract) can be different. In this case, information on the biological source (e.g., potential pathogens, herbicides, pesticides) is warranted in the application so FDA can evaluate the suitability of the biological source as a starting material for drug manufacture (see Attachment 2)."	Clarification Requested: Can the compound extracted from a natural source be a "starting material" for a semi-synthetic drug substance? If so, where is the information on the control of this starting material discussed? Line 689-691 reference an "API starting material (extract) while in line 2001 and 2079, extract is called an "intermediate".
693	~~"The recommendations for starting materials provided in this guidance are for application purposes. See ICH Q7A for recommendations on API starting materials."~~	This line is not needed based on suggested rewording above.
697 1668-1669 2234-2235	Revise the definition of starting material from: ~~"Starting materials for a synthetic drug substance are chemical compounds of defined molecular structure that contribute to the structure of the drug substance."~~ To: **"A starting material for a synthetic drug substance is a chemical compound of defined molecular structure that is incorporated as a significant structural fragment into the structure of the drug substance."**	Consistency with ICHQ7A and with the PhRMA recommendations in "PhRMA Perspectives on Drug Substance Regulatory Filing Issues: Starting Material, Reprocessing, Retesting, and Critical Controls"). The previous, 1987 guidance also included the concept that the starting material is an important structural element of the drug substance. We propose using the word fragment instead of element because the word element may also refer to the Periodic Table of Elements (e.g., carbon, hydrogen, oxygen, etc.), and therefore may be confusing.

698	"A proposed starting material for a synthetic drug substance should be chosen so that sufficient information will be available to FDA on the **drug substance** manufacturing process to evaluate **its** ~~the~~ safety and quality ~~of the drug substance.~~"	Clarification to avoid possible confusion that FDA is requesting information on the starting material manufacturing process.
704	"For semisynthetic processes, information should be provided for the biological source starting material and starting materials of synthetic origin, if there are any. **Note that fermentation-derived drug substances are not included in the scope of this guidance.**"	Clarification that the statement on semi-synthetic drug substances does not apply to fermentation derived drug substances. Fermentation-derived materials are not covered in this guidance.
712	~~"A flow diagram"~~	If this is the flow diagram of the full synthesis it is already provided in Section S2.2. PhRMA does not feel that it is appropriate to provide flow diagram for synthesis describing how Starting Material was made. Either way this bullet item should be deleted.
719	~~"Attachment"~~ should be "**Attachments**".	Correction of typographical error.
738	"A specification should be provided for each material **that is not covered by compendial monograph.**"	It should not be necessary to include a specification sheet for materials included in a compendium (USP, ACS reagents, etc.) This is not required for excipients in drug products and should not be required for raw materials in drug substances.
739	"The specification sheet should list ~~all~~ **critical** tests to which the material will conform and the associated acceptance criteria and should also include a reference to the analytical procedures that will be used to perform each test."	The use of the term "all" is too inclusive. Raw materials are often used in multiple processes (in multiple NDAs), each of which may have special requirements. Each NDA should register those tests that control the quality of that particular drug substance.
745-747	"The tests and acceptance criteria in each specification should be appropriate for the kind of material and its intended use~~, and should be consistent with the quality of the material used to manufacture the batches of drug substance used to establish the specification for the drug substance (see sections VI.A, VI.D, and VI.E).~~"	It should be recognized that at the time of submission of an application only limited number of different lots (and qualities) of solvents, reagents and auxiliary materials may have been used to produce limited number of batches of drug substance. Consistency of specifications with quality of material used is of minor or no importance related to quality of the drug substance. Acceptance criteria have to be related to intended use.

769-772	"In this section of the application, ~~all~~ **only** critical **process controls should be listed. This could include:** operating parameters, ~~environmental controls,~~ process tests **and/or** ~~all~~ tests performed on intermediates **through to final** ~~postsynthesis materials, and unfinished~~ drug substance **for the purpose of determining suitability for downstream processing.** ~~should be listed and~~ Their associated numeric ranges, limits, or acceptance criteria should be identified." Delete rest of this paragraph.	Reworded so that "**intermediates through to final drug substance**" now encompasses everything and there is no need for separate section for **post synthesis material and unfinished drug substance.**
778-788	"For ~~all~~ **these** critical process controls, the associated numeric ranges, limits, or acceptance criteria should be justified and a brief description of the test provided. ~~Any experimental data to support the justification should be included in this section (S.2.4) as well. For critical operating parameters and environmental conditions, numeric ranges, limits, or acceptance criteria typically can be based on the experience gained during the development of the manufacturing process. (See section IV.E for possible exceptions when process validation information is warranted.) Critical process control values from relevant batches (i.e., those for which batch analyses have been provided in S.4.4) should be provided as part of the justification.~~ Justification may be based upon scientific judgment and experience gained during the development of the manufacturing process. Summarized information should be provided. Additional information should be provided in this section (S.2.4) under the following circumstances."	This is information that should be documented in a development report vs. filing. Detailed data to support 'justification' of each critical test or control in the NDA would add to regulatory burden. These should be available for inspection at the manufacturing site.

807	"When the same analytical procedure is used for both the in-process test and the drug substance test, the acceptance criterion for the in-process test should be demonstrated to be **appropriate such that the drug substance will meet its acceptance criterion**.~~identical to or tighter than the acceptance criterion in the drug substance specification.~~"	The option to use in-process testing in place of release would relieve testing for impurities that could be controlled earlier in the process. However, an expectation that the in-process limits would be equal to or tighter than finished API is not acceptable as down stream processing can be shown to sufficiently reduce an impurity.
810	~~"Tests performed in-process in lieu of testing the drug substance should be included in the drug substance specification (S.4.1) and the results of such tests should be included in the batch analysis report (e.g., certificate of analysis))."~~	This would make an extremely cumbersome specification that would be difficult to understand. For example, the level of residual starting material at stage 1 is specified to ensure it is not detected in the drug substance. This requirement would appear to imply that, if this specific chemical or its derivative is not monitored in the API, this information must be contained in the final specification. This is contrary to current practice and will complicate the generation of C of A's enormously (what if portions of two batches of step 1 go into a batch of step 2, and portions of step 2 go into step 3, etc.). This control of intermediate quality against specifications defined in the application should be left to the "quality system" within the manufacturer. It should not be controlled by trying to assimilate all the information on earlier intermediates into the final C of A and specification.
815-817	"When warranted, a specification should be ~~established~~ **provided** for an isolated intermediate to ensure that it has appropriate quality attributes **(e.g., LOD or assay or color or purity)** for further downstream processing. A specification for an intermediate should usually include testing for ~~assay and~~ impurities."	Often the assay is a very gross and ineffective tool for determining the acceptable quality of intermediates. The controls normally focus on specific and total impurities, which is usually a more effective way of controlling quality.

820	"For a ~~semisynthetic~~ drug substance **derived from biological source**, FDA recommends that the following information be provided in S.2.4 for the intermediate used at the beginning of the synthetic operations."	Clarification of the scope of the statement
826	"~~Evidence supporting the chemical structure~~"	The fact that the synthesis makes the proven drug substance pretty much defines the structure.
827	"~~Information concerning impurities~~"	Relevant information should be in the specifications.
839-864	Delete sections on Postsynthesis Materials and Unfinished Drug substance.	Delete these sections. Rewording in the beginning of Section S.2.4 (2nd sentence) now incorporates these materials.
877	Footnote 15 - "**The appropriate parts of** all manufacturing processes should be validated **as defined in ICH Q7A.** However, in most cases, the validation information is reviewed during facility audits."	It is currently not required to validate all parts of manufacturing processes (e.g., formal validation of early process steps is often not performed).
883	"However, it can be warranted when the reprocessing or reworking operation is of the type for which process validation information is submitted when routinely performed **(as described above)** or when the reprocessing or reworking operations have a significant potential to **adversely** affect the identity, strength, quality, purity, or potency of the product (e.g., naturally derived protein drug substances) **It is generally understood that many such situations will occur post-approval."**	To clarify when validation of reprocessing or reworking steps would need to be filed
891	~~"A description to the manufacturing process for the drug substance throughout the various development phases should be provided in S.2.6.~~ The primary focus of this **section is the** description **of the** relationship between **significant** changes **outside normal variabilities** in the manufacturing process or **changes in the** manufacturing site and any associated changes in the chemical or physical properties of the drug substance."	To clarify that this section is not requesting a process development report. The term "changes" as it relates to the process is too broad.

910-911	**"ICH: Q7A"**	Add guidance reference to table
959	"Information can include data from various analytical procedures such as X-ray diffraction (single crystal or powder), thermal analysis (e.g., differential scanning calorimetry, thermal gravimetric analysis, hot-stage microscopy), ~~particle size analysis,~~ or other spectroscopic techniques (e.g. IR, Raman, solid-state NMR, mass)."	Particle size is not an inherent property of the drug substance. Particle size analysis should be taken out of this section and discussed in the justification for the drug substance specification (S.4.5) or in the physicochemical and biological properties section (P.2.2.3) of the drug product.
984, 985	"~~However, screening a variety of solvents with different polarities and hydrogen bonding properties can be valuable for early detection of other polymorphs.~~"	This is a development issue and not a review issue. By including this statement in the guidance, it may be considered an expectation for development rather than a helpful hint.
985	"At an appropriate stage of development, the potential for interconversion of solid state forms should usually be investigated ~~in stability studies.~~"	We agree that this step needs to be done but that there may be alternate methods to primary stability studies. Once it has been shown not to interconvert, the studies should be complete. We should not expect this to be done in an on-going DS stability monitoring program.
992-995	Please provide an example of when further studies on the drug product would be required to conclude whether the physical properties of the DS would have an impact.	For clarification
1009	"The applicant should summarize the actual and potential impurities most likely to arise during manufacture, purification, and storage of the drug substance **based on experience development.**"	The term "most likely to arise" can be interpreted in different ways. Our recommendation would be to focus on impurities observed in development.
1019-1020	~~"Substances that are considered potential impurities but that have not been observed in the batches of drug substance manufactured"~~	There is no value in discussing theoretical impurities that have never occurred during development.

1021-1022	"Impurities that were once present in the **clinical or preclinical** drug substance but that have been eliminated by process modifications"	The discussion should be limited to those that are relevant to the discussion of safety. Early process impurities are not typically discussed/described under S.3.2. It seems more appropriate that these be discussed in S2.6 Process Development and that S.3.2 focus on the final process for commercialization.
1036	"Attempts should be made to identify all impurities found **above the identification threshold (ICH Q3A)** ~~in significant quantities~~ in the drug substance."	Consistency with ICH Q3A (R).
1037	"~~The studies to characterize these impurities should be described.~~"	The techniques used to characterize impurities have previously not been considered a review issue.
1049	"The following are typical of the information that should be provided for impurities **observed in the drug substance:"**	This level of information for **all** actual and potential impurities is not warranted.
1052-1053	"Analytical **technique** ~~procedure~~ used to ~~detect or~~ search for the impurity or potential impurity"	The analytical technique (e.g. LC/MS) should be indicated, but not the detailed analytical procedure.
1057-1058	~~"Structural characterization data and/or other data on the physical or chemical properties of the impurity or potential impurity"~~	Requiring that physical property data be generated for all impurities is unreasonable.
1058	~~"Summary of the route of synthesis or method of preparation if the impurity or potential impurity was independently prepared"~~	Including the route of synthesis of an impurity in an application is not value added.
1060	~~"A summary of the attempts made to identify an impurity if it has not been possible to identify it"~~	This requirement seems excessive; it is not relevant to assuring the quality of the API.

1063 - 1065	"~~A table listing the qualified level of expected impurities with a cross-reference to the appropriate studies (including study numbers and batch numbers). A similar table should be provided in section 3.4 of module~~ 4."	This information is required and more appropriate in other sections of the submission, and at most should be referenced in this section. Particularly with the implementation of electronic, linked submissions, redundancy of information should be avoided.
1085	**"When warranted, a specification should be provided for a** ~~If the~~ drug substance ~~is~~ **that is to be further** processed (e.g., micronized) before it is used to manufacture the drug product.~~, the specification for the unfinished drug substance, if there is one~~, **This specification** should be included in section in S.2.4. However based on manufacturing experience it might be appropriate to reduce testing of either the micronized or the non-micronized form."	Do not want to imply that a specification for unfinished drug substance is <u>always</u> expected.
1108-1110	~~If an analytical procedure will be used only to generate stability data the analytical procedure should be described in S.7.3~~	Either delete this line or clarify when an analytical procedure would only be used for stability and not release.
1111 - 1115	"~~The specifications from the application and/or drug product manufacturer should identify the tests that it will routinely perform and the test results that will be accepted from the drug substance manufacture's certificate of analysis (COA).18 Presentation of information in a tabular format is suggested.~~"	This is a GMP issue not a filing issue which specific tests are done and which are accepted on COA because the drug product manufacturer is always responsible for the quality of the drug substance whether or not the test is actually performed. It isn't always known at the time of submission which tests the manufacturer will eventually accept on vendor COA versus those which will be performed routinely by the manufacturer. This would also delete footnote 18.
1116	"Tests that can be performed in-process (e.g., Process controls or material ~~tests, intermediate tests, postsynthesis material tests, unfinished drug substance~~ tests) in lieu of testing the drug substance (the results of such tests should be included in the batch analysis report (e.g., Certificate of analysis))"	Reworded for alignment with suggested changes in the glossary.

1125	Please provide an example of where the shelf-life criteria would be indicated on the Specification?	This causes concern and could raise substantial problems. Often a tighter in-house spec is used for release but only one regulatory spec is filed.
1127	Revise tables to include better examples.	The tables contain some poor examples of meaningful tests and acceptance criteria for an API.
1128	Table 1 - Add "NMT" before limit for Heavy Metals. Delete the Residual Solvent spec tested at the Intermediate C.	Clarification of examples in table and correction of typo.
1128	Table 1: Remove the requirement to include the Brand for particle size analyzers	Equipment brands should not be included in the filing.
1129	Add footnote: **"This is an example specification and is not intended to imply that these are typical tests and acceptance criteria for synthetized drug substances"**	Comparable to footnote in Table 2.
1154-1156	"If sufficient data (e.g. data from multiple batches, **representative of the** ~~all~~ proposed manufacturing ~~sites and~~ processes~~)~~ are available, a PQIT proposal can be included in the original application."	Sites are expected to make the same quality material; if demonstrated at site A it is a minimal risk that site B would produce different quality material via the same process.
1180	It would be helpful to provide meaningful examples of PQIT tests.	This would help show Agency thinking on this new concept.
1193	"The analytical procedures used for testing a drug substance should be provided. Recommendations on the content and format of analytical procedures submitted ~~in NDAs and ANDAs will be provided in a forthcoming CDER/CBER guidance on Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation~~. **can be found in ICH Q2A."**	There is an ICH guidance on this subject. Do not reference an FDA guidance that has not been published.

1219	"Analytical procedures from any other published source (e.g., ~~another country's compendium,~~ scientific journal) should be provided."	The requirement to provide the analytical procedure from another country's compendium (e.g., EP or JP) is not consistent with the principle contained in footnote 21, in which it is stated that citation of a compendium means the current revision of the cited compendial monograph is used. The requirement to provide the analytical procedure from another country's compendium would mean that the version of the analytical procedure (from e.g. EP) submitted in the NDA would become outdated as soon as the next revision of the EP is effective. PhRMA suggests that for analytical procedures cited from widely available national compendia (e.g., EP, JP, BP, etc.), it not be necessary to provide the text of the monograph or analytical procedure.
1224	"Analytical validation information, including **summary** ~~experimental~~ data (~~e.g.,~~ **and/or a** representative chromatogram(s) with peak identification~~)~~, for the analytical procedures used for testing the drug substance should be provided."	The full analytical validation package can more appropriately be reviewed on-site during an inspection.
1229	"~~Stability data (S.7.3), including d~~Data from stress studies~~,~~ should be used to support the validation of the analytical procedures**, where appropriate.**"	The requirement to use stability data beyond chromatographic stress studies to support validation is unclear.
1229, 1230	"This information should be provided for ~~all~~ **the appropriate** analytical procedures listed in the specification (S.4.1)."	Compendial or certain limit or identity tests should not require presentation of validation data.
1230	"Recommendations on the analytical validation information that should be submitted ~~in NDAs and ANDAs will be provided in a forthcoming CDER/CBER guidance on Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation.~~ **can be found in ICH Q2A"**	There is an ICH guidance on this subject. Do not reference an FDA guidance that has not been published.

1240	"Batch analysis ~~reports (e.g., certificates of analysis (COAs))~~ should be provided for all drug substance batches used for (1) nonclinical studies (i.e., ~~pharmacology and/or~~ toxicology), (2) drug product clinical efficacy and safety, bioavailability, bioequivalence, and (3) primary stability studies.	In the interests of brevity, batch data should be presented as data tables rather than Certificates of Analysis. Also batch analyses are only necessary for toxicology batches, not pharmacology batches.
1245	**"Batch analysis data may be presented either as individual batch analysis reports or as collated batch analysis tables.** The batch analysis ~~reports and collated batch analyses~~ data should include a description of the batches. This information can be presented (1) with the batch data as space permits or (2) in a separate table with only the batch identity being included with the batch data. "	Tabular presentation of data may be more useful and submission of both individual reports and tabular data is redundant with little if any added value.
1257	Test results should be expressed numerically or qualitatively (e.g., white ~~crystalline~~ powder), as appropriate.	Technical accuracy (Can't assess crystallinity visually)
1258, 1259	"We discourage the use terms such as conforms or meets specification **for tests which have defined numerical limits.**"	It should be acceptable to report conforms or passes for identity and similar tests, provided the specification is included in the batch analysis table.
1262-1264	"The batch analysis reports should include results from ~~all~~ **the** tests ~~performed on the batch, including tests~~ that are ~~not~~ part of the proposed specification."	There may be examples where additional results are needed to justify the proposed specification. That data should be provided in section S.4.5. As currently stated in the draft guidance this could be over inclusive.

1266-1275	~~"A summary of any changes in the analytical procedures should be provided if the analytical procedures (1) changed over the course of generating the batch analyses data and/or (2) are different from the analytical procedure included in S.4.2. The summary should identify when an analytical procedure changed, the differences between the analytical procedures, and the impact of the differences with respect to the data being reported. For example, a summary could state that the solvent system for the assay was changed on December 15, 1999, from A to B so that impurities Y and Z that co-elute using System A could be quantitated separately. If there are significant differences in the analytical procedures (e.g., different fundamental principles such as titration and HPLC), a more detailed summary describing the changes may be warranted."~~	Delete here and cover applicable changes under the stability section S.7.
1282	"However, collated data should be provided for ~~assay and~~ impurities..."	Assay data, in general would not appear to require collation.
1307-1311	"However, exclusion of a test that is normally performed on a type of drug substance~~, one that is recommended in~~ **according to ICH Q6A or another** relevant FDA guidance, ~~or one that was reported in the batch analyses (S.4.4)~~ should be justified."	Include reference to ICH Q6A.
1322-1323	"However, it is not certain if the same type of results will continue to be observed for production batches because (1) limited data are available at the time the application is submitted and/or (2) the manufacturing process for production batches will be different ~~(e.g., scale, equipment)~~ from that used to produce the batches used to support the application and the effect, if any, of the differences has yet to be characterized."	Scale and equipment are given as examples for a difference in a manufacturing process that could produce uncertainty about the appropriateness of the specification. Scale or equipment changes alone should not generally be considered as impacting the quality of the drug substance.

1337	"Results from nonclinical (pharmacology and/or toxicology), clinical, and stability studies and manufacturing and analytical capability should be considered when proposing acceptance criteria. Proposed acceptance criteria can include a reasonable allowance for analytical and manufacturing variability. **The primary basis for the acceptance criteria should be the safety and efficacy data not process capability**. The justification should discuss the basis of the proposed acceptance criteria from the perspectives of available data and analytical and manufacturing capability and variability. Furthermore, any statistical approaches that are used to establish the acceptance criteria should be described."	PhRMA is concerned that basing specifications on process capability rather than safety information will result in unnecessarily tight specifications that lead to higher cost of manufacture with no added value to the patient (for example tightening down to process capability on residual solvent when that is much lower than ICH Guidance).
1351	"This uncertainty often occurs when (1) there are limited data available at the time the application is submitted and/or (2) the manufacturing process for production batches will be different ~~(e.g., scale, equipment)~~ from that used to produce the batches used to support the application and the effect, if any, of the differences has yet to be characterized."	Scale and equipment are given as examples for a difference in a manufacturing process that could produce uncertainty about the appropriateness of the specification. Scale or equipment changes alone should not generally be considered as impacting the quality of the drug substance.
1371-1372	Revise the following sentence from: "Acceptance criteria for residual solvents should generally be based upon manufacturing capability." to "Acceptance criteria for residual solvents should generally be based **on safety (per ICH Q3C and VICH GL18), analytical variability, and** manufacturing ~~capability~~ **variability**."	At the time of submission, it is unusual to have manufactured enough batches to assess manufacturing capability. ICH Q3C and VICH GL18 provide guidance on safe levels of residual solvents. Analytical variability should also be considered when setting specifications.
1386	"The justification should explain the scientific reasons why a stability indicating procedure is not **used** ~~viable or warranted~~ (e.g., inorganic salts) and, when appropriate, which analytical procedures complement the assay procedure by qualitatively and/or quantitatively monitoring impurities, including degradants."	Flexibility to select one procedure over another should be retained provided it is based on sound scientific judgment. Applicant should not have to demonstrate a particular procedure is not viable when another procedure can provide the same information.

1395	"Information on the **primary** reference standards ~~or reference materials used for testing of the drug substance~~ used for testing of the drug substance (active moiety) should be provided."	Secondary standards which are assessed against the primary standard are covered under internal GMP controlled procedures.
1396	"When the **drug substance** reference standard is not from an official source, it should be ~~fully~~ **appropriately** characterized **(see Section S3.1 Elucidation of Structure and Other Characteristics)."**	Clarify that this sentence is only to the drug substance reference standard. Also change "fully" to "appropriately" because some things such as particle size characterization are not value added for a reference standard.
1401-1402	"A list of ~~any available~~ **impurity** reference standards ~~for impurities and intermediates~~ **that are reference in drug substance analytical procedures** should be included in S.5."	Information should only be required in the application for reference standards that are needed to perform drug substance testing specified in the application.
1409 - 1411	"A description of the container closure system for the drug substance should be provided, including the identity of materials of construction of each primary packaging component and its specification **where appropriate (e.g., when a unique or non-standard material is used in the container closure system)**."	The request to provide specifications for commonly used packaging components (e.g. HDPE or LDPE bags) is considered unnecessary. It should continue to be sufficient to simply state the material of composition for most container closure systems, unless a unique system is required.
1412	"~~For nonfunctional packaging secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided."~~	No information should be necessary for non-functional secondary packaging components; this requirement would result in the need for a post approval submission to change the nonfunctional secondary package even though this change would have no potential to adversely impact the quality of the API.

1414-1417	"The suitability of the container closure system should be discussed with respect to **compatability and safety of the primary packaging component(s) and**~~, for example, choice of materials,~~ protection from moisture and light~~, compatibility of the materials of construction with the drug substance, including sorption to the container and leaching, and/or safety of materials of construction.~~ **A reference to the appropriate indirect food additive regulation is typically considered sufficient to establish the safety of the materials of construction."**	Consistency with the FDA Guidance Container Closure Systems for Packaging Human Drugs and Biologics (May 1999)
1418	The following statement should be added: **"Smaller versions that simulate the actual container closure system may be used in stability studies."**	Both the FDA guidance Container Closure Systems for Packaging Human Drugs and Biologics (May 1999) and ICH Q1A (R2) provide for the use of simulated packaging. It would be helpful to include the information in this guidance for completeness.
1428	'The types of studies conducted, protocols used, and the results of the studies should be summarized. The discussion should include for example (1) a summary of stability batches tested, storage conditions used, attributes tested, ~~shelf life~~ acceptance criteria, test schedule, amount of data available, and analysis of data (including a summary of the statistical analysis if performed) and (2) conclusions regarding the label storage conditions **if special restrictions on storage are required** ~~and retest or expiration dating period, as appropriate~~."	The term retest period is applicable for most drug substances. Shelf life implies an expiration date, which is not widely applied. Also labeled storage conditions are only needed on drug substances that require special conditions, e.g. refrigeration. If stability data show that the drug substance is stable at the climatic zone conditions where it will be shipped, no special storage statements are required.
1437	"A postapproval ~~stability protocol and~~ stability commitment should be provided."	We realize that this is in ICH CTD however, this is a new expectation to provide the stability protocol in the filing. We believe that the stability protocol should be available for review during a GMP inspection. Its inclusion in the filing does not add value.

1444	"An applicant should propose a retest or expiration dating period and ~~appropriate~~ label storage conditions **(if restrictions on storage conditions are needed)** for the drug substance. There should be a direct link between the proposed retest or expiration dating period and proposed label storage condition **(if restrictions on storage conditions are needed)** and the demonstrated stability characteristics of the drug substance."	If stability data show that the drug substance is stable at the climatic zone conditions where it will be shipped, no special storage statements are required.
1451	The meaning of the term 'intermediate studies' is not clear.	FDA Should clarify that this means intermediate conditions for testing as shown in Q1(R) pg. 17 and not stability testing of process intermediates.
1465	"A summary of changes in analytical procedures **that affect the reported result(s)** should be provided if the analytical procedure was changed over the course of generating the stability data."	Not all analytical changes need be discussed; some are very minor.
1482-1483	"Stability data to support holding times ~~for intermediates or~~ during processing should also be provided in this section **for proteins, if appropriate** ~~when warranted (e.g. certain proteins).~~"	For drug substances manufactured by chemical synthesis, specifications, including tests for assay and impurities, are established for intermediates. These specifications ensure that the intermediate is fit for use in the subsequent step.
1490, 1491	"~~Any~~ results from drug substance stress testing should be provided in this section of the application**, or referenced from other sections.**"	Stress studies performed as part of method validation seem to be better reported directly in S.4.3 and referenced in S.7.3 if relevant to the stability studies for the API or the specifications. The word "any" should be deleted from this sentence. Results should be provided for the stress studies as described in ICH Q1A (R2).
1494	"The information should be used, as appropriate, to support the validation of analytical procedures (S.4.3), the impurities acceptance criteria and/or characterization of expected impurities (S.3.2, S.4.1), justification of the drug ~~product~~ **substance** specification (S.4.5), and stability summary and conclusions (S.7.1 and S.7.3)."	Typographical error

1496	~~"In June 1998 (63 FR 31224), the Agency made available a draft revision of this guidance entitled Stability Testing of Drug Substances and Drug Products. When finalized, this revision will be the primary reference source on stability testing of drug substances and drug products."~~	Reference to Draft Guidance from 1998 that has not yet been finalized adds to confusion. Reference should be to ICH Q1A.
1505	Delete "~~(e.g., A.1 drug substance then drug product, followed by A.2)~~." Replace with: "(e.g. A.1.1 drug substance, A.1.2 drug product, A.2.1 drug substance, A.2.2 drug product)."	Clarification
1553	Adventitious Agents Safety Evaluation	It would seem that this section might be handled in separate guidance.
1571-1574	Delete these lines.	Again the guidance is inconsistent in providing guidance to applicants of biotechnology-derived protein drug substances when this guidance is not intended for such drug substances.
1588	"Certifications and/or **documentation** ~~certificates~~ relating to the **safe** use of bovine-derived materials should be provided, as appropriate. **Current requirements include certification that bovine-derived materials are not sourced** ~~and sourcing of materials~~ from BSE countries as defined by the U.S. Department of Agriculture (9 CFR 94.11)."	Requirements are expected to change continually on this issue, and guidance here should be kept general and cross-reference up-to-date and specific requirements provided elsewhere.
1628	"Executed **Batch** ~~Production~~ Records"	To be consistent with ICH M4Qs
2140-2146	Final Intermediate: "~~In reference to synthetic and semisynthetic drug substances, the last compound synthesized before the chemical reaction that produces the molecule or ion responsible for the physiological or pharmacological action of the drug substance. The chemical reaction that transforms the final intermediate into a form of the drug substance involves more than a change in salt form (including a salt with hydrogen or coordination bonds) or other noncovalent derivatives (such as~~	Change this definition to be consistent with BACPAC I.

	~~complex chelates or clathrates).~~" **"For the purposes of this guidance, the last compound synthesized before the reaction that produces the drug substance. The final step forming the new drug substance involves covalent bond formation; ionic bond formation (i.e. making the salt of a compound) does not qualify. Consequently, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate."**	
2151	"~~In process~~ Material Tests: Measures used to assess the quality attributes of an intermediate, postsynthesis material, or unfinished drug substance and/or their suitability for use in the manufacturing process."	
2157	Add the following definition for interim acceptance criteria: **"Acceptance criteria proposed at time of submission with a proposal for reevaluation as more data is available."**	Clarification
2168	~~"Intermediate Tests: Measures used to assess the quality attributes of an intermediate and/or its suitability for use in the manufacturing process"~~	Covered under "Material Test"
2184-94	Delete definition of postsynthesis materials.	
2192	~~"Postsynthesis Material Tests: Measures used to assess the quality attributes of a postsynthesis material and/or its suitability for use in the manufacturing process"~~	Covered under "Material Test"

2195	"**In-**Process Controls: **Checks performed** ~~An all-inclusive term used to describe the controls used~~ during production **in order** to monitor and, if appropriate, **to** adjust the process and/or to ensure **that the** ~~an~~ intermediate ~~with an established specification~~ or the drug substance will conform to its respective specification. ~~The term includes operating parameters, environmental controls, process tests, intermediate tests, postsynthesis materials tests, and unfinished drug substance tests."~~	Change to provide consistency with ICH Q7A.
2195	**Add** **"Process Controls: see In-Process Controls"**	For Clarification
2200	~~"Process Tests: Measures used to monitor and assess the performance of the process (e.g., a test to evaluate reaction progress)"~~	Covered under In-Process Controls
2202	Add a definition of Propinquity.	Clarity
2203	"Reaction Step: A unit operation or number of unit operations that effect a change in the molecular structure of a starting material or intermediate **or another type of transformation (e.g. salt formation) that has a demonstrated purifying effect.** More than one reaction step can take place sequentially in a single -reaction vessel."	See comments on line 1755.
2211	"Retest Period**:** The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification ~~and then used immediately.~~ A batch of drug substance can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a retest period. The same may	It has been common industry practice to establish subsequent retest dates based on sound scientific data. This practice must not be prohibited by a definition which fails to allow for flexibility based on good sound science.

	be true for certain antibiotics (ICH Q1A or VICH GL3)."	
2231-2232	Specification sheet should be defined separately.	Clarification
2240	Add the following definition for sunset test: **"A test that may be dropped from the drug substance specification after an agreed number of production batches have met certain criteria."**	Clarification
2248	~~"Unfinished Drug Substance Tests: Measures used to assess the quality attributes of an unfinished drug substance and/or its suitability for use in the manufacturing process"~~	Covered under "Material Test"